SMALL MOLECULES FOR THE TREATMENT OF PRIMARY CANCER AND CANCER METASTASIS

[0001] This Application is a continuation application of U.S. patent application Ser. No. 16/267,106, filed Feb. 4, 2019, which is a continuation application of U.S. patent application Ser. No. 15/544,056, filed Jul. 17, 2017 (issued as U.S. Pat. No. 10,214,529), which is a national phase application under 35 U.S.C. § 371 of International Application No. PCT/US2016/013645, filed Jan. 15, 2016, which claims priority to U.S. Provisional Application Ser. No. 62/104,705 filed Jan. 17, 2015, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The bone is the most common site of metastasis in patients with advanced cancers including breast and prostate cancers (Jin et al. (2011) *Int. J. Cancer* 128, 2545-2561; Kohno, (2008) *Int. J Clin. Oncol.* 13, 18-23). Bone metastases are major, potentially fatal complications in patients with advanced cancers. Almost all patients with skeletal metastases have significantly decreased quality of life due to intense pain, pathological fractures, spinal cord compression, and metabolic complications (Welch et al. (2003) *J. Musculoskelet. Neuronal Interact.* 3, 30-38). In fact, postmortem studies have shown that over 70% of breast cancer patients exhibited skeletal metastases, and only 20% of these patients are still alive five years after the discovery of the metastases (Roodman (2004) *N. Engl. J Med* 350, 1655-1664; Welch et al. (2003) *J. Musculoskelet. Neuronal Interact.* 3, 30-38). The high affinity that cancer has for bone is explained by the "seed-and-soil hypothesis", which was proposed over a century ago (Paget (1889) *Lancet* 1, 571-573). It reveals that bone tissues are preferred sites of cancer metastasis due to their microenvironment, which provides a fertile setting in which tumor cells can grow. Many features, such as increased blood flow as well as the release of growth factors from cells in the bone matrix, account for the frequency of bone metastases (van der Pluijm et al. (2001) *J. Bone Miner. Res.* 16, 1077-1091). Thus far, the critical factors and mechanisms responsible for bone metastases are largely unknown.

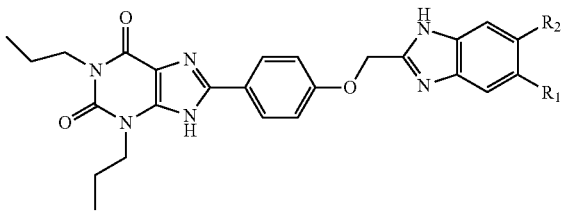
[0003] Bisphosphonate drugs are used to treat bone cancer metastasis and result in decreased tumor growth, reduced bone destruction, and reduced pain (Brown and Guise (2007) *Cur. Osteopor. Rep.* 5, 120-127). Bisphosphonate therapy is associated with adverse side effects, which include atrial fibrillation; arthralgia and osteonecrosis of the jaw; and ophthalmic, dermatologic and renal complications; as well as medication-induced fractures (Junquera et al. (2009) *Am. J. Otolaryngol.* 30, 390-395; Truong et al. (2010) *J. Am. Acad. Dermatol.* 62, 672-676). Despite advances in the diagnosis and treatment of bone metastasis from solid tumors, the mechanism of how bisphosphonate treatment inhibits bone metastasis at the molecular level remains to be established.

[0004] Adenosine receptor antagonist analog compounds can be used for treatment of cancer (WO2014074529). However, there still remains a need for additional non-hydrolysable ATP analog compounds and adenosine receptor antagonists.

SUMMARY

[0005] Certain embodiments are directed to non-hydrolysable ATP analogs that inhibit migration and growth of cancer cells. The term non-hydrolysable ATP analog refers to an ATP analog that is not effectively hydrolyzed by ATPase, i.e., the analog is hydrolyzed, if at all, at a rate that is less than 5, 1, or 0.1% of the rate of ATP hydrolysis by ATPase. Certain embodiments are directed to various chemical analogs of the non-hydrolysable ATP analog adenosine 5'-[γ-thio]triphosphate (ATPγS). These chemicals inhibit cancer cell migration and growth. Certain embodiments are directed to chemical analogs of the non-hydrolysable adenosine ATP analog 5'-[γ-thio]triphosphate (ATPγS) having the general formula of Formula: I, including compounds P1-P6 (Table 1)

Formula I



where R_1 and R_2 are selected independently from hydrogen (H), cyano (CN), C1 to C3 alkyl, halogen (fluoro (F), chloro (Cl), bromo (Br), or iodo (I)), or a trifluoromethyl (CF_3). In certain aspects R1 is selected from hydrogen, cyano, C1 to C3 alkyl, halogen (fluoro (F), chloro (Cl), bromo (Br), or iodo (I)), or a trifluoromethyl, and R2 is hydrogen or fluoro. In a further aspect R1 is cyano and R2 is H, R1 is H and R2 is H, R1 is trifluoromethyl and R2 is H, R1 is fluoro and R2 is H, R1 is methyl and R2 is H, and R1 is fluoro and R2 is fluoro.

[0006] Certain embodiments are directed to administration of one or more compounds of Formula Ito treat cancer. The compounds can be administered alone or in combination with other anti-cancer therapies.

[0007] Adenosine exposure can promote cancer cell growth and migration, and adenosine is produced by the metabolism of ATP. Certain embodiments are directed to a number of chemical analogs of adenosine receptor antagonist 8-Ethoxy-9-ethyl-9H-purin-6-amine (ANR94, A2A antogonist). These compounds are inhibitors of cancer cell migration and growth. In certain aspects the chemical analogs of adenosine receptor antagonist 8-Ethoxy-9-ethyl-9H-purin-6-amine have a general formula of Formula II, including compounds P7-P10 (Table 1)

Formula II